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# THE ADDICTION LIABILITY OF SYNTHETIC SUBSTITUTES FOR CODEINE

## (Project Description)

Request to the Office of Naval Research for the Renewal of
Contract NAonr-25-59, NR 101-149

1. Background Information

Since 1951 the National Institute of Mental Health Addiction Research Center has been carrying on a project with the object of discovering synthetic substitutes for codeine which would be as safe as that drug with respect to toxicity and addiction liability, and which would also be as effective as codeine as an antitussive, antidiarrheal, and analgesic agent. The project has been financed partly by funds from the Office of Naval Research. This description constitutes a request for renewal of the project for the period 1 July 1961 to 30 June 1962.

Initially the project was undertaken because codeine was the most widely used narcotic drug in both civilian and military medical practice. Since codeine is derived from opium, or made from morphine derived from opium, this situation made it necessary for the United States to stockpile opium in event of war. The facilities of the NIMH Addiction Research Center were not

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sufficient to carry out the work, in addition to evaluation of potent new analgesics submitted by the Committee on Drug Addiction and Narcotics of the National Research Council, unless additional funds were supplied through the Department of Defense.

2. Work Accomplished to Date

More than 60 compounds have been examined in the nine years the project has been operating. Two nonaddictive, antitussive drugs (dextromethorphan and narcotine) were found. Ethoheptazine (Zactirin) and d-propoxyphene (Darvon, Lilly) were found to be less addictive than codeine and both are analgesics clinically, but unfortunately they are less potent and more toxic than codeine. Diphenoxylate (R-1132) is a potent diarrheal agent which is less addictive than codeine.

During the current year we have examined nine new drugs. Two of these, phenyramidol and carisoprodol, are reputed to be intermuncial blockers that are effective in relieving pain due to muscular spasm. Neither drug possesses morphine-like addictiveness, and therefore both have potentially reduced the need for codeine as an analgesic.

One new drug, 1-(p-Chlor-phenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (NIH-7672A or ARC I-K-1) is of great interest. Clinically I-K-1 is more closely related to papaverine than to morphine. In small

animals it induces a rather typical spectrum of morphine-like effects and its analgesic potency in animals is almost equal to that of codeine. In former morphine addicts only minor subjective and objective effects occurred following oral administration of as much as 600 mg orally or 180 mg intravenously. The drug was only 1/7th as potent as codeine intramuscularly in suppressing abstinence from morphine. Following abrupt withdrawal of I-K-1 after oral administration of doses running up to as much as 1800 mg daily for two months, no symptoms of abstinence were reported. Obviously I-K-1 is much less addictive than is codeine. Despite this, preliminary clinical work indicates that the compound may be as effective as codeine in relieving pain. If this is true, then I-K-1 represents the greatest degree of dissociation between analgesic potency and addictiveness yet achieved. Unfortunately I-K-1 is soluble only in highly acid solution and therefore is very irritating on injection.

Biochemical studies on the rate of excretion, metabolism, and fate of codeine were undertaken during the year. Codeine and its metabolic products were isolated during administration and following discontinuation of codeine to former morphine addicts, using paper chromatography. The project is not complete since final quantitation is to be carried out, using a gas chromatograph which has not yet been obtained. Among the objects of the project are to determine what proportion of the codeine is excreted as morphine and what proportion as norcodeine. This portion of the project is to be extended to some of the promising codeine substitutes.

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3. Need for Continuation of the Project

Although a great deal of progress has been made and substitutes are now available for all purposes for which codeine is used, we still have no single drug which is as effective and nontoxic as codeine. The analgesics, Darvon and ethoheptazine, are not nearly as effective as is codeine; clinical investigation of I-K-1 is not complete and furthermore that drug cannot be given by injection. No single synthetic yet discovered incorporates all the properties of codeine. Further more data is needed on the excretion, distribution, metabolism and fate of these various synthetic substitutes.

4. Work Proposed

Between 1 July 1931 and 1 July 1932 we propose to test the clinical pharmacology and addictiveness of d-3-Dimethylamino-1-diphenylbutyl ethyl sulfone; 1, 2-Dimethyl-3-phenyl-3 pyrollidinol propionate ester; 1-Dimethylamino-3-phenylindane, 1-2'-hydroxy-2, 5, 9-trimethyl-6, 7-benzmorphan; l-2'Methoxy-5, 9-dimethyl-2 phenethyl-6, 7-benzmorphan; and alpha-dl-3-Acetoxy-6-methylamino-4, 4-diphenylheptane. All of these compounds have been recommended for study by the Committee on Drug Addiction and Narcotics, National Research Council.

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In addition the project on the excretion of codeine and its metabolites will be completed as soon as a gas chromatograph is obtained and placed in operation. Following this, studies on the metabolism and fate of I-K-1, R-1132, and propoxyphene will be initiated.

5. Methods

The methods used are the standard addiction liability testing methods of the NIMH Addiction Research Center. These tests are accepted as legal standards by the Committee on Drug Addiction and Narcotics, and have been described in previous project descriptions which should be consulted for details.

The biochemical methods used are also standard and involve separation of the drugs and their metabolites by extraction with differential solvents at various pH, separation from impurities by paper chromatography, and identification by a variety of end reactions including gas chromatography, ultraviolet spectrophotometry and fluorescence measurements.

6. Evaluation of Data

Evaluation of the data has been covered in previous project descriptions.

7. Location of the Project

The work will be carried out at the NIMH Addiction Research Center, PHS Hospital, Lexington, Ky. This institution provides the two necessary facilities for the type of work to be undertaken: 1) a pool of patients who will volunteer for experiments with drugs, and 2) strict environmental control, which prevents introduction of drugs other than those under study into the experimental situation.

Complete biochemical facilities are also available.

8. Experimental Personnel

The work will be carried out under the direction of Harris Isbell, M.D., Director, NIMH Addiction Research Center. This investigator has had 16 years experience in research on narcotic drug addiction and has an extensive bibliography in the field. He will be assisted by two other experienced physicians, Drs. H.F. Fraser and Abraham Wikler, both of whom have done extensive research in addiction and have many publications. The part-time services of a biochemist, neuropharmacologist, and research psychologist are also available. A special ward for the conduct of these studies has been made available by the hospital and has been operating for more than eight years.

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9. Estimated Cost

The estimated costs are shown on the attached sheet. The amount of money requested is the same as that requested for fiscal year 1961.

Harris Isbell, M. D.
Director

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Attachment

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